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NOTICE OF ALLOWANCE AND FEE(S) DUE

7590

01/12/2010

STEVEN L. HIGHLANDER
FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TX 78701

EXAMINER

SALIMI, ALI REZA

ART UNIT

PAPER NUMBER

1648

DATE MAILED: 01/12/2010

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/203,078 | 12/01/1998 | SHUYUAN ZHANG | INRP-081 | 3754 |

TITLE OF INVENTION: METHOD FOR THE PRODUCTION AND PURIFICATION OF ADENOVIRAL VECTORS

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|----------------|--------------|---------------|---------------------|----------------------|------------------|------------|
| nonprovisional | NO | \$1510 | \$0 | \$0 | \$1510 | 04/12/2010 |

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

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If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail

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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

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7590 01/12/2010

**STEVEN L. HIGHLANDER
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600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TX 78701**

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE-FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| |
|--------------------|
| (Depositor's name) |
| (Signature) |
| (Date) |

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| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|------------------|----------|----------------|
| SALIMI, ALI REZA | 1648 | 435-005000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/147; Rev 03-02 or more recent) attached. Use of a **Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

1

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY AND STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
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4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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SHUYUAN ZHANG

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3754

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01/12/2010

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EXAMINER

SALIMI, ALI REZA

ART UNIT

PAPER NUMBER

1648

DATE MAILED: 01/12/2010

Determination of Patent Term Extension under 35 U.S.C. 154 (b)

(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 1634 day(s). Any patent to issue from the above-identified application will include an indication of the 1634 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability**Application No.**

09/203,078

Applicant(s)

ZHANG ET AL.

Examiner

A R. Salimi

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERIT IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to ____.
2. ☒ The allowed claim(s) is/are 2-31, 33-46 and 48-62.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
(a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
(b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Attorney De La Paz on 01/07/2010.

The application has been amended as follows:

Canceled Claims 1 and 47.

2. (Currently amended) ~~The process of claim 30A~~ A process for preparing adenovirus, the process comprising:

- (a) preparing a culture of producer cells in a selected media;
- (b) infecting producer cells in the culture with the adenovirus in a bioreactor system, a microcarrier culture system, a multiplate culture system, a perfused packed bed reactor system, or a microencapsulation culture system, wherein the producer cells are infected with the adenovirus between late-log phase and stationary phase of growth; and
- (c) harvesting adenovirus from the cell culture.

3. (Currently amended) ~~The process of claim 1, A~~ A process for preparing adenovirus, the process comprising:

- (a) preparing a culture of producer cells in a selected media;
- (b) infecting producer cells in the culture with the adenovirus, wherein the producer cells are infected between mid-log phase of growth and stationary phase of growth and, wherein the producer cells are essentially homogeneous with respect to the phase of cell growth; and

(c) harvesting adenovirus from the cell culture.

4. (Currently amended) The process of claim $[[1]]2$, wherein the producer cells are perfused for at least a portion of the time that the cells are cultured.
5. (Original) The process of claim 4, wherein the producer cells are perfused at a rate that will maintain a glucose level of between about 0.5 and about 3.0 gm glucose/liter.
6. (Original) The process of claim 5, wherein the producer cells are perfused at a rate that will maintain a glucose level of between about 0.7 and about 2.0 gm glucose/liter.
7. (Original) The process of claim 6, wherein the producer cells are perfused at a rate that maintains a glucose level of between about 1 and about 1.5 gm glucose/liter.
8. (Currently amended) The process of claim $[[1]]2$, wherein the producer cells are seeded into the culture medium and allowed to attach to a culture surface for between about 3 hours and about 24 hours prior to infection with adenovirus.
9. (Currently amended) The process of claim $[[1]]2$, wherein the culture medium is at least partially recirculated during the adenovirus infection step.
10. (Currently amended) The process of claim $[[1]]2$, wherein the culture medium is seeded with between about 0.5×10^4 and about 3×10^4 cells/cm².
11. (Original) The process of claim 10, wherein the culture medium is seeded with between about 7.5×10^3 and about 2.0×10^4 cell/cm².
12. (Original) The process of claim 11, wherein the culture medium is seeded with between about 9×10^3 and 1.5×10^4 cells/cm².

13. (Currently amended) The process of claim [[1]]2, wherein the harvested adenovirus is subjected to purification and placed into a pharmaceutically acceptable composition.
14. (Original) The process of claim 13, the adenovirus is purified by steps which include chromatography.
15. (Original) The process of claim 14, wherein the chromatography step involves subjecting the adenovirus to more than one chromatographic separations.
16. (Original) The process of claim 14, wherein the chromatography step involves subjecting the adenovirus to only one chromatographic separation.
17. (Original) The process of claim 16, wherein the chromatographic separation includes ion-exchange chromatography.
18. (Currently amended) The process of claim [[1]]2, wherein said adenovirus is a replication-deficient adenovirus encoding a selected gene operably linked to a promoter.
19. (Original) The process of claim 18, wherein said replication deficient adenovirus is lacking at least a portion of the E1 region.
20. (Original) The process of claim 19, wherein said producer cells complement the growth of replication deficient adenovirus.
21. (Currently amended) The process of claim [[1]]2, wherein said producer cells are selected from the group consisting of 293, PER.C6, 911 and IT293SF cells.
22. (Original) The process of claim 21, wherein said producer cells are 293 cells.
23. (Original) The process of claim 18, wherein said selected gene is selected from the group consisting of antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense

fms, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl*, antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, *zac1*, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF G-CSF, *mda-7*, thymidine kinase or p53.

24. (Original) The process of claim 23, wherein said selected gene is a p53 gene.
25. (Original) The process of claim 18, wherein said promoter is an SV40 IE, RSV LTR, β -actin, CMV-IE, adenovirus major late, polyoma F9-1, or tyrosinase promoter.
26. (Currently amended) The process of claim [[1]]2, wherein the adenovirus is harvested by steps that include lysing the producer cells by means other than freeze-thaw.
27. (Original) The process of claim 26, wherein the producer cells are lysed by means of a detergent lysis.
28. (Original) The process of claim 26, wherein the producer cells are lysed by means of autolysis.
29. (Currently amended) The process of claim [[1]]2, further comprising purifying the harvested adenovirus to obtain a purified adenovirus composition having one or more of the following properties:
 - (a) a virus titer of between about 1×10^9 and about 1×10^{13} pfu/ml;
 - (b) a virus particle concentration between about 1×10^{10} and about 2×10^{13} particles/ml;
 - (c) a particle:pfu ratio between about 10 and about 60;
 - (d) having less than 50 ng BSA per 1×10^{12} viral particles;
 - (e) between about 50 pg and 1 ng of contaminating human DNA per 1×10^{12} viral particles,

- (f) a single HPLC elution peak consisting essentially of 97 to 99% of the area under the peak.
30. (Currently amended) The process of claim [[1]]3, wherein infecting producer cells in the culture with the adenovirus occurs in a bioreactor system, a microcarrier culture system, a multiplate culture system, a perfused packed bed reactor system, or a microencapsulation culture system.
31. (Previously presented) The process of claim 29, further comprising formulating the purified adenovirus composition into a pharmaceutically acceptable composition.
32. (cancelled)
33. (Previously presented) The process of claim 31, wherein the pharmaceutically acceptable composition is administered to a subject.
34. (Previously presented) The process of claim 33, wherein the subject is a mammal.
35. (Previously presented) The process of claim 34, wherein the mammal is a human or a mouse.
36. (Previously presented) The process of claim 33, wherein administering is intravenously, intradermally, intramuscularly, intraarterially, intralesionally, percutaneously, subcutaneously, or by inhalation.
37. (Previously presented) The process of claim 36, wherein administering is intratumorally.
38. (Currently amended) The process of claim [[1]]2, wherein the adenovirus is a recombinant adenovirus.

39. (Currently amended) The process of claim [[1]]2, wherein the producer cells are cultured in a bioreactor system.
40. (Previously presented) The process of claim 39, wherein the bioreactor system is a stirred tank reactor.
41. (Previously presented) The process of claim 39, wherein the bioreactor system is a airlift reactor.
42. (Previously presented) The process of claim 39, wherein the bioreactor system is a sparged bioreactor.
43. (Currently amended) The process of claim [[1]]2, wherein the producer cells are cultured in a microcarrier culture system.
44. (Currently amended) The process of claim [[1]]2, wherein the producer cells are cultured in a multiplate cell culture system.
45. (Currently amended) The process of claim [[1]]2, wherein the producer cells are cultured in a perfused packed bed reactor system.
46. (Currently amended) The process of claim [[1]]2, wherein the producer cells are cultured in a microencapsulation culture system.
47. (Cancelled)
48. (Currently amended) A method of claim [[47]]50, wherein the further improvement comprises infecting the cultured producer cells in a bioreactor system, a microcarrier culture system, a multiplate culture system, a perfused packed bed reactor system, or a microencapsulation culture system.

49. (Currently amended) A method of claim [[47]]50, wherein the improvement further comprises harvesting adenovirus from the cell culture.

50. (Currently amended) ~~A method of claim 47 for producing adenovirus that includes culturing producer cells and infecting the cultured producer cells with an adenovirus, wherein the improvement comprises infecting said producer cells with the adenovirus when the cells in culture are between late-log phase of growth and stationary phase of growth.~~

51. (Currently amended) A method of claim [[47]]50, wherein said adenovirus is a recombinant adenovirus.

52. (Previously presented) A method of claim 51, wherein said recombinant adenovirus comprises a selected gene operably linked to a promoter.

53. (Currently amended) A method of claim [[47]]50, wherein said adenovirus is a replication-deficient adenovirus.

54. (Previously presented) A method of claim 53, wherein said replication deficient adenovirus is lacking at least a portion of the E1 region.

55. (Currently amended) A method of claim [[47]]50, wherein said producer cells complement the growth of replication deficient adenovirus.

56. (Previously presented) A method of claim 55, wherein said producer cells are selected from the group consisting of 293, PER.C6, 911 and IT293SF cells.

57. (Previously presented) A method of claim 56, wherein said producer cells are 293 cells.

58. (Currently amended) ~~A method of claim 47~~ In a method for producing adenovirus that includes culturing producer cells and infecting the cultured producer cells with an adenovirus, wherein the improvement comprises infecting said producer cells with the adenovirus when the

cells in culture are between mid-log phase of growth and stationary phase of growth and;
~~wherein~~ the producer cells are essentially homogeneous with respect to the phase of cell growth.

59. (Previously presented) A method of claim 52, wherein said selected gene is selected from the group consisting of antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense *fms*, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl* antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF G-CSF, mda-7, thymidine kinase or p53.

60. (Previously presented) A method of claim 59, wherein said selected gene is a p53 gene.

61. (Previously presented) A method of claim 52, wherein said promoter is an SV40 IE, RSV LTR, β -actin, CMV-IE, adenovirus major late, polyoma F9-1, or tyrosinase promoter.

62. (Previously presented) A method of claim 49, wherein the improvement further comprises purifying the harvested adenovirus to obtain a purified adenovirus composition having one or more of the following properties:

- (a) a virus titer of between about 1×10^9 and about 1×10^{13} pfu/ml;
- (b) a virus particle concentration between about 1×10^{10} and about 2×10^{13} particles/ml;
- (c) a particle:pfu ratio between about 10 and about 60;
- (d) having less than 50 ng BSA per 1×10^{12} viral particles;
- (e) between about 50 pg and 1 ng of contaminating human DNA per 1×10^{12} viral particles,
- (f) a single HPLC elution peak consisting essentially of 97 to 99% of the area under the peak.

Claims 2-31, 33-46, 48-62 are allowed. Claims have be renumbered from 1-59.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to A. R. Salimi whose telephone number is (571) 272-0909. The examiner can normally be reached on Monday-Friday from 9:00 Am to 6:00 Pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. The Official fax number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/A R Salimi/

Primary Examiner, Art Unit 1648

01/28/2010

